FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR
220171US0PCT	10/088088

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/06623	26 September 2000	1 October 1999

TITLE OF INVENTION
AMIDE COMPOUNDS

APPLICANT(S) FOR DO/EO/US
Kiyotaka ITO et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

Notice of Priority/ Form PTO-1449
PCT/IB/304

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/088088	PCT/JP00/06623	220171US0PCT

24. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

	CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	2 - 20 =	0	x $18.00	**$0.00**
Independent claims	2 - 3 =	0	x $84.00	**$0.00**
Multiple Dependent Claims **(check if applicable).**			☐	**$0.00**
TOTAL OF ABOVE CALCULATIONS =				**$890.00**
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**
SUBTOTAL =				**$890.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				**$0.00**
TOTAL NATIONAL FEE =				**$890.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**
TOTAL FEES ENCLOSED =				**$890.00**
			Amount to be: refunded	$
			charged	$

a. ☒ A check in the amount of **$890.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

22850

Surinder Sachar
Registration No. 34,423

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

March 21 2002
DATE

DESCRIPTION

AMIDE COMPOUNDS

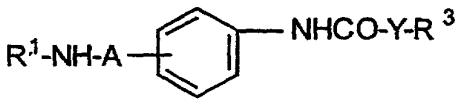
TECHNICAL FIELD

The present invention relates to novel amide compounds and salts thereof. More particularly, it relates to novel amide compounds and salts thereof which have pharmacological activities such as 5-hydroxytryptamine (5-HT) antagonism and the like.

Said amide compounds and their salts are useful as a 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse (e.g., with cocaine, ethanol, nicotine and benzodiazepines), schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus in human being and animals.

BACKGROUND ART

With regard to the state of the art in this field, for example, the following amide compounds are disclosed in Japanese Patent Kokai No. Hei 11(1999)-130750.

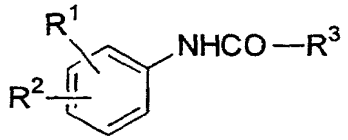


wherein R^1 is quinolyl, quinazolinyl, isoquinolyl or pyridyl group, R^3 is phenyl, cyclo(lower)alkyl, indolyl, lower alkyl-indazolyl or 2,3-dihydroindolyl group, Y is single bond, lower alkylene or lower alkenylene group, and A is lower alkylene group.

DISCLOSURE OF INVENTION

As a result of an extensive study, the inventors of the present invention found some amide compounds which have strong pharmacological activities.

The amide compounds of the present invention are novel and can be represented by the formula (I):



(I)

wherein

R^1 is an N-containing heterocyclic group selected from an imidazolyl, a triazolyl, a pyridyl, a pyridazinyl, a pyrimidinyl and a pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R^2 is a hydrogen atom or a lower alkyl group, and

R^3 is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group,

provided that

(1) the imidazolyl group for R^1 is substituted with one or more alkyl groups, when R^3 is a phenyl group substituted thienyl; an indolyl group substituted with lower alkyl; or carbazolyl group,

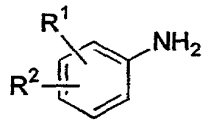
(2) the imidazolyl group for R^1 is substituted with two lower alkyl groups, when R^3 is a phenyl group substituted with halophenyl, or

(3) R^1 is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, a 4-(lower alkyl)-imidazol-1-yl or a 4,5-di(lower alkyl)-imidazol-1-yl group, when R^3 is fluorenyl group.

Suitable salts of the compounds (I) are conventional non-toxic pharmaceutically acceptable salts and may include salts with inorganic bases, for example, alkali metals (e.g. sodium or potassium), alkaline earth metals (e.g. calcium or magnesium) or ammonia ; salts with organic bases, for example, organic amines (e.g. triethylamine, pyridine, picoline, ethanolamine, triethanolamine, dicyclohexylamine or N,N'-dibenzylethylenediamine); inorganic acid addition salts (e.g. hydrochloride, hydrobromide, hydriodide, sulfate or phosphate); organic carboxylic or sulfonic acid addition salts (e.g. formate, acetate,

trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate or p-toluenesulfonate); salts with basic or acidic amino acids (e.g. arginine, aspartate or glutamate); and the like, and preferable examples thereof are the inorganic or organic acid addition salts.

According to the present invention, the object compounds (I) can be prepared by the following process:



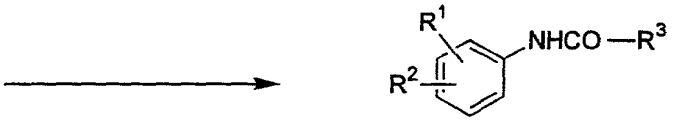
(II)

or its reactive derivative at the amino group or a salt thereof

+ R^3-COOH

(III)

or its reactive derivative at the carboxy group or a salt thereof



(I)

or a salt thereof

wherein R^1, R^2 and R^3 are each as defined above.

In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope are explained in detail in the following.

The term "lower" is intended to mean 1 to 6 carbon atoms, preferably 1 to 4 carbon atoms, unless otherwise indicated.

Suitable lower alkyl groups and lower alkyl moieties in the halo(lower)alkyl groups may include straight or branched ones, having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and hexyl, and preferably the ones having 1 to 4 carbon atom(s), among which the most preferred one is methyl.

Suitable halo(lower)alkyl groups may include lower alkyl

groups substituted with one or more halogen atoms such as fluoromethyl, fluoroethyl, fluoropropyl, trifluoromethyl, chloromethyl, dichloromethyl, chloroethyl, chloropropyl, bromomethyl, bromoethyl, bromopropyl, iodomethyl, iodoethyl, iodopropyl, and the like.

Suitable halophenyl groups may include fluorophenyl, difluorophenyl, chlorophenyl, dichlorophenyl, trichlorophenyl, bromophenyl, dibromophenyl, tribromophenyl, iodophenyl, and the like.

When imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl groups for R^1 is substituted with two or more lower alkyl groups, said lower alkyl groups may be the same or different from each other.

And also, when indolyl group for R^3 is substituted with two or more lower alkyl groups and/or two or more halo(lower)alkyl groups, said lower alkyl groups and halo(lower)alkyl groups may be the same or different from each other.

The process for preparing the object compounds (I) is explained in detail in the following.

The object compound (I) and its salt can be prepared by reacting a compound (II) or its reactive derivative at the amino group or a salt thereof with a compound (III) or its reactive derivative at the carboxy group or a salt thereof.

Suitable reactive derivatives at the amino group of the compound (II) may include Schiff's base type imine or its tautomeric enamine type isomer formed by the reaction of the compound (II) with a carbonyl compound such as aldehyde, ketone or the like; a silyl derivative formed by the reaction of the compound (II) with a silyl compound such as bis(trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea or the like; a derivative formed by the reaction of a compound (II) with phosphorus trichloride or phosgene, and the like.

Suitable salts of the compound (II) and its reactive derivative can be referred to those as exemplified for the compound(I).

Suitable reactive derivatives at the carboxy group of the compound (III) may include the acid halides, acid anhydrides, activated

amides, activated esters and the like.

Suitable examples of such reactive derivatives may be the acid chloride; the acid azide; the mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid or halogenated phosphoric acid], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid], aliphatic carboxylic acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid] or aromatic carboxylic acid [e.g. benzoic acid]; symmetrical acid anhydride; activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2N^+$=CH-] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester or 8-quinolyl thioester], or ester with an N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide or 1-hydroxy-1H-benzotriazole], and the like.

The reactive derivative can optionally be selected from the above according to the kind of the compound (III) to be used.

Suitable salts of the compound (III) and its reactive derivative may be the base salts such as alkali metal salts [e.g. sodium salt or potassium salt], alkaline earth metal salts [e.g. calcium salt or magnesium salt], ammonium salts, organic base salts [e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt or N,N'-dibenzylethylenediamine salt], or the like, and acid addition salts as exemplified for the compound (I).

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol or ethanol], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any

other organic solvent which does not adversely influence the reaction, or a mixture thereof.

In this reaction, when the compound (III) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N-N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide; N,N'-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate, etc.]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)-isoxazolium hydroxide intramolecular salt; benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower) alkylmorpholine, N,N-di(lower)alkylbenzylamine or the like,

The reaction is usually carried out under cooling to warming, although the reaction temperature is not critical.

The object compound (I) of the present invention can be isolated and purified in a conventional manner, for example extraction, precipitation, fractional crystallization, recrystallization, chromatography and the like.

The object compound (I) thus obtained can be converted to its

corresponding salt by the conventional method.

The object compound (I) and salts thereof may include solvates [e.g., enclosure compound (e.g., hydrate, etc.)].

Among the starting compounds (II) and (III), novel compounds can be prepared by the method described in the following Examples or similar method thereto.

In order to exhibit the usefulness of the present invention, the activities of the compounds (I) are shown in the following.

Test method:

[^{3}H]-mesulergine binding

The affinity of the test drugs for the 5-HT_{2c} binding site can be determined by assessing their ability to displace [^{3}H]-mesulergine in the rat prefrontal cortex. The method employed was similar to that of Pazos et al, 1984.

The membrane suspension (500 µl) was incubated with [^{3}H]-mesulergine (1 nM) in Tris HCl buffer containing $CaCl_2$ 4 mM and ascorbic acid 0.1 % (pH 7.4) at 37 ℃ for 30 minutes. Non-specific binding was measured in the presence of mianserin (1 µM). 30 nM spiperone was used to prevent binding to 5-HT_{2A} sites. Test drugs (10^{-6} M) were added in a volume of 100 µl. The total assay volume was 1000 µl. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting.

The IC_{50} values were determined using a four parameter logistic program (DeLean 1978) and the pKi (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$Ki = \frac{IC_{50}}{1+C/Kd}$$

Ki = inhibition constant
C = concentration of [^{3}H]-mesulergine
Kd = affinity of mesulergine for 5-HT_{2c} binding site.

Test Compounds:

(1) N-(1-Methyl-1H-indol-5-yl)-N'-(3-pyridyl)urea
(reference compound)
(2) N-(3-(pyridin-3-yl)phenyl)-9H-fluorene-1-carboxamide (Example 1)
(3) N-(3-(pyrimidin-5-yl)phenyl)-9H-fluorene-1-carboxamide (Example 2)
(4) N-(3-(pyridazin-4-yl)phenyl)-9H-fluorene-1-carboxamide (Example 6)

Test result:

Compound	Inhibition (%)
(1)	21
(2)	74
(3)	92
(4)	64

As shown in above, the object compounds (I) of the present invention exhibit pharmacological activities such as 5-HT antagonism, especially, 5-HT_{2c} antogonism, and therefore are useful as 5-HT antagonist for treating or preventing central nervous system (CNS) disorders such as anxiety, depression, obsessive compulsive disorders, migraine, anorexia, Alzheimer's disease, sleep disorders, bulimia, panic attacks, withdrawal from drug abuse (e.g., with cocaine, ethanol, nicotine and benzodiazepines), schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus, and the like.

For therapeutic or preventive administration, the object compounds (I) of the present invention are used in a form of conventional pharmaceutical preparation which contains said compound as an active ingredient, in admixture with pharmaceutically acceptable carriers such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral and external

administration. The pharmaceutical preparations may be in a solid form such as tablet, granule, powder or capsule, or in a liquid form such as solution, suspension, syrup, emulsion or lemonade.

If needed, there may be included in the above preparations auxiliary substances, stabilizing agents, wetting agents and other commonly used additives such as lactose, citric acid, tartaric acid, stearic acid, magnesium stearate, terra alba, sucrose, corn starch, talc, gelatin, agar, pectin, peanut oil, olive oil, cacao butter, ethylene glycol and the like.

While the dosage of the compound (I) may vary from and also depend upon the age, conditions of the patient, kind of diseases or conditions, kind of the compound (I) to be applied, etc., in general, 0.01-500 mg of the compound (I) may be administered to a patient per day.

An average single dose of about 0.05 mg, 0.1 mg, 0.25 mg, 0.5 mg, 1 mg, 20 mg, 50 mg, 100 mg of the compound (I) may be used in treating the diseases.

The following Examples are given for illustrating the present invention, but it is to be noted that the scope of the present invention is not limited by these Examples.

BEST MODE FOR CARRYING OUT THE INVENTION

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Example 1

To a suspension of 3-(pyridin-3-yl)aniline (0.17 g) and pyridine (0.24 ml) in dichloromethane (3 ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.23g) in dichloromethane (2 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in

dichloromethane to give N-(3-(pyridin-3-yl)phenyl)-9H-fluorene-1-carboxamide (0.317 g, 87.6 %).

NMR (DMSO-d_6, δ): 4.23 (2H, s), 7.3 - 7.7 (7H, m), 7.78 (1H, d, J= 7.7Hz), 7.8 - 8.1 (4H, m), 8.18 (1H, s), 8.60 (1H, d, J = 4.8Hz), 8.88 (1H, s), 10.47 (1H, s)

APCI- Mass m/z : 363 (M^++1).

Example 2

To a suspension of 3-(pyrimidin-5-yl)aniline (0.17g) and pyridine (0.24ml) in dichloromethane (3ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.23g) in dichloromethane (5 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[3-(pyrimidin-5-yl)phenyl]fluorene-1-carboxamide (0.222 g, 61.2 %).

NMR (DMSO-d_6, δ): 4.23 (2H, s), 7.3 - 7.5 (2H, m), 7.5-7.7 (4H, m), 7.78 (1H, d, J= 8.0Hz), 7.8 - 8.1 (2H, m), 8.13 (1H, d, J = 7.7 Hz), 8.21 (1H, s), 9.12 (2H, s), 9.23 (1H, s), 10.51 (1H, s)

APCI- Mass m/z : 364 (M^++1).

Example 3

To a suspension of 9H-carbazole-1-carboxylic acid (106 mg) and 1-hydroxybenzotriazole (81 mg) in dichloromethane (2 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and the mixture was stirred for 15 minutes. After adding 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and 4-dimethylaminopyridine (92 mg), the mixture was stirred for 60 hours. The residue was evaporated under reduced pressure and purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-9H-carbazole-1-carboxamide (101 mg, 53.2 %).

NMR (DMSO-d_6, δ): 2.37 (3H, s), 3.59 (3H, s), 6.90 (1H, s), 7.2-7.6 (5H,

m), 7.71 (1H, d, J = 8.0Hz), 7.89 (1H, d, J = 8.2 Hz), 7.96 (1H, s), 8.11 (1H, d, J = 7.4 Hz), 8.18 (1H, d, J =7.7 Hz), 8.38 (1H, d, J = 7.7 Hz), 10.47 (1H, s), 11.49 (1H, s)

APCI- Mass m/z : 381 (M^{+}+1).

Preparation 4(1)

To a suspension of 3,6-dichloropyridazine (2.98 g), 3-nitrophenylboronic acid (1.67 g) and tetrakis(triphenylphosphine)-palladium (578 mg) in 1,2-dimethoxyethane (30 ml) was added an aqueous solution of sodium carbonate (2M, 15 ml), and the mixture was stirred at 80 ℃ for 3 hours. The mixture was diluted with ethyl acetate, and then washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 30 % ethyl acetate in n-hexane to give 3-chloro-6-(3-nitro-phenyl)-pyridazine (0.246g, 10.4 %).

NMR (DMSO-d_6, δ): 7.88 (1H, t, J = 8.1Hz), 8.13 (1H, d, J = 9.0Hz), 8.41 (1H, dt, J = 6.8Hz, 1.2Hz), 8.54 (1H, d, J =9.0Hz), 8.6-8.8 (1H,m), 8.97 (1H, t, J = 1.2Hz)

APCI- Mass m/z : 236 (M^{+}+1).

Preparation 4(2)

A suspension of 3-chloro-6-(3-nitro-phenyl)pyridazine (0.34 g) in tetrahydrofuran (5 ml) and ethanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 100 mg) under hydrogen atmosphere for 10 hours. The catalyst was filtered off and the filtrate was evaporated under reduced pressure. The residue was diluted with ethyl acetate and an aqueous solution of sodium hydrogen carbonate. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3-pyridazin-3-yl-phenylamine (155 mg, 62.8 %).

NMR (DMSO-d_6, δ): 5.29 (2H, broad s), 6.72 (1H, t, J = 2.8Hz), 7.1-8.0 (4H, m), 8.04 (1H, d, J = 8.6Hz), 9.16 (1H, dd, J = 5.0Hz, 1.6Hz)

APCI- Mass m/z : 172 (M^{+}+1).

Example 4

To a suspension of 1-fluorenecarboxylic acid (184 mg) and oxalyl chloride (0.2 ml) in dichloromethane (4 ml) was added N,N-dimethylformamide (0.01 ml), and the mixture was stirred for 2 hours. The resultant solution was evaporated to give a crude acid chloride. To a suspension of 3-pyridazin-3-yl-phenylamine (150 mg) and pyridine (0.21 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (5 ml) followed by stirring for an hour. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-(3-(pyridazin-3-yl)phenyl)-9H-fluorene-1-carboxamide (44 mg, 13.8 %).

NMR (DMSO-d_6, δ): 4.24 (2H, s), 7.3-7.5 (2H, m), 7.5-7.7 (3H, m), 7-7-7.9 (3H, m), 7.99 (1H, dd, J = 7.0Hz, 1.8Hz), 8.1-8.3 (2H, m), 8.70 (1H, t, J = 3.6Hz), 9.24 (1H, dd, J = 4.9Hz, 1.5Hz), 10.54 (1H, s)

APCI- Mass m/z : 364 (M^++1).

Preparation 5(1)

To a suspension of 2-chloropyrazine (1.14 g), 3-nitrophenylboronic acid (2.00 g) and tetrakis(triphenylphosphine)-palladium (346 mg) in 1,2-dimethoxyethane (30 ml) was added an aqueous solution of sodium carbonate (2M, 12 ml) followed by stirring at 80 ℃ for 18 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol and collected by filtration. The obtained product was washed with methanol and diisopropyl ether and dried to give 2-(3-nitrophenyl)pyrazine (1.78g, 88.6 %).

NMR ($CDCl_3$, δ): 7.26 (1H, s), 7.67 (1H, t, J = 8.0Hz), 8.36 (1H, dt, J =7.7 Hz, 1.5 Hz), 8.63 (1H, d, J =2.4Hz), 8.70 (1H, t, J = 4.0Hz), 8.93 (1H, t, J

=4.0Hz), 9.13 (1H, t, J =1.5Hz)
APCI- Mass m/z : 202 (M^{+}+1).

Preparation 5(2)

A suspension of 2-(3-nitrophenyl)pyrazine (500 mg) in tetrahydrofuran (5ml) and ethanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 200 mg) under hydrogen atmosphere for 6 hours. The catalyst was filtered off and the filtrate was evaporated. The residue was crystallized from dichloromethane-diisopropyl ether to give 3-(pyrazin-2-yl)aniline (410 mg, 96.5 %).
NMR ($CDCl_3$, δ): 3.82(2H, s), 6.81 (1H, dt, J =6.0Hz, 1.2Hz), 7.3-7.6 (3H, m), 8.49 (1H, d, J =2.5Hz), 8.60 (1H, t, J = 1.3Hz), 9.00 (1H, d, J= 1.5Hz)
APCI- Mass m/z : 171 (M^{+}+1).

Example 5

To a suspension of 3-(pyrazin-2-yl)aniline (0.12g) and pyridine (0.17ml) in dichloromethane (3ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.16g) in dichloromethane (3 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-(3-(pyrazin-2-yl)phenyl)-9H-fluorene-1-carboxamide (0.193 g, 76.0 %).
NMR (DMSO-d_6, δ): 4.24 (2H, s), 7.3 - 7.7 (5H, m), 7.79 (1H, d, J= 7.6Hz), 7.8 - 8.1 (3H, m), 8.13 (1H, d, J = 6.8Hz), 8.6-8.7 (2H, m), 8.76 (1H, t, J = 1.2Hz), 9.23 (1H, d, J = 1.5Hz), 10.52 (1H, s)
APCI- Mass m/z : 364 (M^{+}+1).

Preparation 6(1)

A suspension of 3-nitrobenzyl cyanide (1.62 g), glyoxylic acid monohydrate (1.38 g) and potassium carbonate (3.59 g) in methanol (20 ml) was stirred for 5 hours. The precipitate was collected by filtration,

washed with dichloromethane and dried. The precipitate was suspended in water and stirred for an hour. The insoluble material was collected by filtration and dried to give 3-cyano-3-(3-nitro-phenyl)-acrylic acid potassium salt (2.18 g, 85.2 %).

ESI-Mass m/z : 217 ($M-K^+$)

NMR (DMSO-d_6, δ): 7.36 (1H, s), 7.73 (1H, t, J =8.0Hz), 8.10 (1H, d, J = 7.9Hz), 8.24 (1H, d, J =7.9HZ), 8.62 (1H, s)

Preparation 6(2)

To a suspension of 3-cyano-3-(3-nitro-phenyl)-acrylic acid potassium salt (1.28 g) in formic acid (10 ml) and water (1 ml) was added sulfuric acid (1ml), and the mixture was refluxed for 3 hours. After cooling, the mixture was poured into water. The resulting precipitate was collected by filtration and dried to give 3-(3-nitro-phenyl)-furan-2,5-dione(0.69 g).

NMR ($CDCl_3$, δ): 7.24 (1H, d, J =8.9Hz), 7.76 (1H, d, J = 8.1Hz), 8.3-8.5 (2H, m), 8.81 (1H,s)

APCI- Mass m/z : 220 (M^++1).

Preparation 6(3)

To a suspension of 3-(3-nitro-phenyl)-furan-2,5-dione (673 mg) in acetic acid (7 ml) was added hydrazine hydrate (0.18 ml), and the mixture was refluxed for 5 hours. The mixture was poured into water. The resulting precipitate was collected by filtration and dried to give 4-(3-nitro-phenyl)-1,2-dihydro-pyridazine-3,6-dione (0.68 g, 95.0%).

NMR (DMSO-d_6, δ): 7.43 (1H, s), 7.6-8.4 (3H, m), 8.81 (1H, s), 11.04 (1H, broad s), 12.31 (1H, broad s)

APCI- Mass m/z : 234 (M^++1).

Preparation 6(4)

A suspension of 4-(3-nitro-phenyl)-1,2-dihydro-pyridazine-3,6-dione (668 mg) in phosphorus oxychloride (6 ml) was refluxed for 2 hours. The mixture was concentrated under reduced pressure and diluted with ethyl acetate. The solution was washed with an aqueous

solution of sodium hydrogen carbonate and brine and dried over magnesium sulfate. The organic layer was evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with dichloromethane to give 3,6-dichloro-4-(3-nitro-phenyl)pyridazine (385 mg, 49.9 %).

NMR ($CDCl_3$, δ): 7.26(1H, s), 7.57 (1H, s), 7.76 (1H, t, J =8.1Hz), 7.86 (1H, d, J =7.9 Hz), 8.4-8.6 (2H, m)

APCI- Mass m/z : 270 (M^++1).

Preparation 6(5)

A suspension of 3,6-dichloro-4-(3-nitro-phenyl)pyridazine (0.19 g) and sodium hydrogen carbonate (147 mg) in tetrahydrofuran (2 ml) and ethanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 100 mg) under hydrogen atmosphere for 3 hours. The catalyst was filtered off, and the filtrate was evaporated. The residue was diluted with ethyl acetate and an aqueous solution of sodium hydrogen carbonate. The separated organic layer was washed with brine and dried over potassium carbonate. The organic layer was evaporated under reduced pressure to give 3-(pyridazin-4-yl)phenylamine (106 mg, 88.3 %).

NMR (DMSO-d_6, δ): 5.35 (2H, broad s), 6.72 (1H, t, J = 7.6Hz), 7.0-7.2 (2H, m), 7.20 (1H, t, J= 8.0Hz), 7.85 (1H, dd, J = 5.6Hz, 2.4Hz), 9.23 (H, d, J = 5.6Hz), 9.49 (1H, s)

APCI- Mass m/z : 172 (M^++1).

Example 6

To a suspension of 1-fluorenecarboxylic acid (120 mg) and oxalyl chloride (0.12 ml) in dichloromethane (2.5 ml) was added N,N-dimethylformamide (0.01 ml) and the mixture was stirred for 2 hours. The resultant solution was evaporated to give a crude acid chloride. To a suspension of 3-(pyridazin-4-yl)phenylamine (98 mg) and pyridine (0.14 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (5 ml), and the mixture was stirred for an hour. The mixture was diluted with dichloromethane

and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-(3-(pyridazin-4-yl)-phenyl)-9H-fluorene-1-carboxamide (133 mg, 63.9 %).

NMR (DMSO-d_6, δ): 4.23 (2H, s), 7.3-7.7 (6H, m), 7.79 (1H, d, J =7.0Hz), 7.9-8.1 (3H, m), 8.14 (1H, d, J = 6.9Hz), 8.34 (1H, s), 9.32 (1H, d, J=5.5Hz), 9.60(1H, s), 10.56(1H, s)

APCI- Mass m/z : 364 (M^++1).

Preparation 7

To a solution of 2-(3-methoxycarbonylphenyl)thiophene (1.29 g) in methanol (15 ml) and tetrahydrofuran (5 ml) was added an aqueous solution of sodium hydroxide (1N, 8.87 ml) followed by stirring for 2 hours at 60℃. To the mixture was added hydrochloric acid (1N, 10 ml). The resulting precipitate was collected by filtration and dried to give 2-(3-carboxyphenyl)thiophene (1.13g, 93.4 %).

NMR (DMSO-d_6, δ): 7.17 (1H, t, J = 4.4 Hz), 7.5-7.7 (3H, m), 7.87 (1H, d, J = 7.8Hz), 7.93 (1H, d, J = 7.8Hz), 8.15 (1H, s), 13.19 (1H, broad s)

ESI- Mass m/z : 203 (M^+-1).

Example 7

To a suspension of 3-(2-thienyl)benzoic acid (102 mg) and oxalyl chloride (0.2 ml) in dichloromethane (2 ml) was added N,N-dimethylformamide (0.01 ml), and the mixture was stirred for an hour. The resultant solution was evaporated to give a crude acid chloride. To a suspension of 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and pyridine (0.12 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (2 ml), and the mixture was stirred for 12 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The

residue was purified with a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-3-(thiophen-2-yl)benzamide (140 mg, 74.9 %).
NMR (DMSO-d_6, δ): 2.36 (3H,s), 3.59 (3H, s), 6.89 (1H, s), 7.1-7.3 (2H, m), 7.44 (1H, t, J = 7.9Hz), 7.6-7.8 (3H, m), 7.79 (1H, d, J = 8.0Hz), 7.8-8.0 (3H, m), 8.19 (1H, s), 10.45 (1H, s)
APCI- Mass m/z : 374 (M^++1).

Example 8

To a suspension of 9H-carbazole-1-carboxylic acid (422 mg) and 1-hydroxybenzotriazole (324 mg) in dichloromethane (10 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (575 mg), and the mixture was stirred for 15 minutes. After adding 3-(pyrimidin-5-yl)aniline (360 mg) and 4-dimethylaminopyridine (367 mg), the mixture was stirred for 48 hours. The residue was evaporated under reduced pressure and purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-(3-(pyrimidin-5-yl)-phenyl)-9H-carbazole-1-carboxamide (314 mg, 43.1 %).
NMR (DMSO-d_6, δ): 7.20(1H, t, J = 7.4Hz), 7.33 (1H, t, J = 7.7Hz), 7.42 (1H, t, J = 7.6Hz), 7.58 (2H, d, J =5.1Hz), 7.72 (1H, d, J =8.0Hz), 7.9-8.1 (1H, m),8.17 (2H, dd, J =7.4Hz, 4.0HZ), 8.35 (1H, s), 8.39 (1H, d, J =7.5Hz), 9.15 (2H, s), 9.23 (1H, s), 10.56 (1H, s), 11.54 (1H, s)
APCI- Mass m/z : 365 (M^++1).

Example 9

To a suspension of 9H-carbazole-1-carboxylic acid (148 mg) and 1-hydroxybenzotriazole (114 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg) and the mixture was stirred for 15 minutes. After adding 3-(1,2,4-triazol-1-yl)aniline (123 mg) and 4-dimethylaminopyridine (128 mg), the mixture was stirred for 24 hours. The mixture was evaporated under reduced pressure and purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[3-(1,2,4-

triazol-1-yl)-phenyl]-9H-carbazole-1-carboxamide (103 mg, 41.5 %).
NMR (DMSO-d_6, δ): 7.20(1H, t, J = 7.3Hz), 7.32 (1H, t, J = 7.5Hz), 7.42 (1H, t, J = 7.3Hz), 7.5-7.7 (2H, m), 7.73 (1H, d, J =8.2 Hz), 7.86 (1H, d, J = 7.3Hz), 8.1-8.3 (2H, m), 8.28 (1H, s), 8.40 (1H, d, J =7.5 Hz), 8.61 (1H, s), 9.30 (1H, s), 10.64 (1H, s), 11.57 (1H, s)
APCI- Mass m/z : 354 (M^++1).

Preparation 10(1)

To a suspension of 2-bromo-5-methoxycarbonylthiophene (1.11 g) and phenylboronic acid (0.79 g) and tetrakis(triphenylphosphine)-palladium (289 mg) in 1,2-dimethoxyethane (10 ml) was added an aqueous solution of sodium carbonate (2M, 6.5 ml) followed by stirring at 80℃ for 18 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration, washed with methanol and diisopropyl ether and dried to give 2-methoxycarbonyl-5-phenylthiophene (918 mg, 84.2 %).
NMR ($CDCl_3$, δ): 3.84 (3H, s), 7.4-7.6 (3H, m), 7.62 (1H, d, J = 4.0HZ), 7.7-7.9 (2H, m), 7.81 (1H, d, J =4.0Hz)
APCI- Mass m/z : 219 (M^++1).

Preparation 10(2)

To a solution of 2-methoxycarbonyl-5-phenylthiophene (437 mg) in methanol (5 ml) and tetrahydrofuran (5 ml) was added an aqueous solution of sodium hydroxide (1N, 3 ml) followed by stirring for 2 hours. To the mixture was added hydrochloric acid (1N, 5 ml). The precipitate was collected by filtration and dried to give 5-phenylthiophene-2-carboxylic acid (397 mg, 97.1 %).
NMR (DMSO-d_6, δ): 7.3-7.5 (3H, m), 7.58 (1H, d, J =3.9Hz), 7.6-7.8 (3H, m), 13.15 (1H, broad s)
ESI- Mass m/z : 203 (M^+-1).

Example 10

To a suspension of 5-phenylthiophene-2-carboxylic acid (102 mg) and oxalyl chloride (0.2 ml) in dichloromethane (2 ml) was added N,N-dimethylformamide (0.01 ml), and the mixture was stirred for an hour. The resultant solution was evaporated under reduced pressure to give a crude acid chloride. To a suspension of 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and pyridine (0.12 ml) in dichloromethane (2 ml) was dropwise added a solution of the acid chloride obtained above in dichloromethane (2 ml) followed by stirring for 12 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-5-phenyl-thiophene-2-carboxamide (155 mg, 82.9 %).

NMR (DMSO-d_6, δ): 2.36 (3H,s), 3.57 (3H, s), 6.89 (1H, s), 7.17 (1H, d, J =7.8HZ), 7.4-7.6 (4H, m), 7.64 (1H, d, J = 4.0Hz), 7.7-7.9 (4H, m), 8.04 (1H, d, J = 4.0Hz), 10.34 (1H, s)

APCI- Mass m/z : 374 (M^++1).

Preparation 11(1)

To a suspension of 5-bromopyrimidine (1.59 g), 4-methyl-3-nitrophenylboronic acid (2.35 g) and tetrakis(triphenylphosphine)-palladium (578 mg) in 1,2-dimethoxyethane (20 ml) was added an aqueous solution of sodium carbonate (2M, 13 ml) followed by stirring at 80℃ for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitated was collected by filtration, washed with methanol and diisopropyl ether and dried to give 5-(4-methyl-3-nitrophenyl)-pyrimidine (918 mg, 84.2 %).

NMR ($CDCl_3$, δ): 2.56 (3H, s), 7.68 (1H, d, J =8.0Hz), 8.10 (1H, dd, J = 8.0Hz, 1.8Hz), 8.42 (1H, d, J =1.8Hz), 9.23 (3H, s)

APCI- Mass m/z : 216 (M^++1).

Preparation 11(2)

A suspension of 5-(4-methyl-3-nitrophenyl)-pyrimidine (258 mg) in tetrahydrofuran (5ml) and methanol (5 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 130 mg) under hydrogen atmosphere for 4 hours. The catalyst was filtered off and the filtrate was evaporated to give 5-(3-amino-4-methylphenyl)pyrimidine(410 mg, 96.5 %).

NMR ($CDCl_3$, δ): 2.11 (3H, s), 5.05 (2H, s), 6.87 (1H, dd, J =7.6Hz, 1.8Hz), 6.96 (1H, d, J =1.8Hz), 7.07 (1H, d, J = 7.6Hz), 8.98 (2H, s), 9.12 (1H, s)

APCI- Mass m/z : 186 (M^++1).

Example 11

To a suspension of 9H-carbazole-1-carboxylic acid (148 mg) and 1-hydroxybenzotriazole (114 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg), and the mixture was stirred for 15 minutes. After adding 5-(3-amino-4-methylphenyl)pyrimidine (136 mg) and 4-dimethylaminopyridine (128 mg), the mixture was stirred for 24 hours. The mixture was evaporated under reduced pressure and the residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[6-methyl-3-(pyrimidin-5-yl)-phenyl]-9H-carbazole-1-carboxamide (89 mg, 33.6 %).

NMR (DMSO-d_6, δ): 2.40 (3H, s), 7.20(1H, t, J = 7.4Hz), 7.32 (1H, t, J = 7.6Hz), 7.4-7.6 (2H, m), 7.6-7.8 (2H, m), 7.96 (1H, s), 8.17 (2H, d, J =7.7 Hz), 8.39 (1H, d, J =7.6Hz),9.17 (2H, s), 9.19 (1H, s), 10.19 (1H, s), 11.46 (1H, s)

APCI- Mass m/z : 379 (M^++1).

Example 12

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-

dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 18 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[3-(1,2-dimethyl-1H-imidazol-5-yl)-phenyl]-3-methyl-2-trifluoromethyl-1H-indole-7-carboxamide (130 mg,63.1 %).
NMR (DMSO-d_6, δ): 2.36 (3H, s), 2.44 (3H, s), 3.57 (3H, s), 6.88 (1H, s), 7.17 (1H, d, J = 8.0Hz), 7.31 (1H, d, J = 8.0Hz), 7.45 (1H, t, J =7.8 Hz), 7.82 (1H, d, J =8.0Hz), 7.9-8.1 (3H, m), 10.50 (1H, s), 11.48 (1H, s)
APCI- Mass m/z : 413 (M^++1).

Example 13

To a suspension of 2,3-dimethylindole-7-carboxylic acid (95 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 18 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-[3-(1,2-dimethyl-1H-imidazol-5-yl)-phenyl]-2,3-dimethyl-1H-indole-7-carboxamide (73 mg, 40.8 %).
NMR (DMSO-d_6, δ): 2.18 (3H, s), 2.37 (6H, s), 3.57 (3H, s), 6.88 (1H, s), 7.06 (1H, d, J =7.6HZ), 7.15 (1H, d, J =10.1 Hz), 7.44 (1H, d, J = 7.9Hz), 7.61 (1H, d, J =7.6Hz), 7.72 (1H, d, J = 7.3Hz), 7.85 (1H, d, J =8.2 Hz), 7.92 (1H, s), 10.30 (1H, s), 10.76 (1H, s)
APCI- Mass m/z : 359 (M^++1).

Example 14

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 3-(pyrimidin-5-yl)aniline (86 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 18 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[3-(pyrimidin-5-yl)-phenyl]-3-methyl-2-trifluoromethyl-1H-indole-7-carboxamide (106 mg, 53.5 %).

NMR (DMSO-d_6, δ): 2.45 (3H, s), 7.31 (1H, t, J = 7.7Hz), 7.4-7.6 (2H, m), 7.9-8.1 (3H, m), 8.26 (1H, s), 9.13 (2H, s), 9.23 (1H, s), 10.59 (1H, s), 11.49 (1H, s)

APCI- Mass m/z : 397 (M^++1).

Example 15

To a suspension of 3-(4-fluorophenyl)benzoic acid (151 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (131 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg) and 4-dimethylaminopyridine (43 mg). The mixture was stirred at ambient temperature for 18 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-4'-fluoro-biphenyl-3-carboxamide (240 mg, 88.9 %).

NMR (DMSO-d_6, δ): 2.36(3H, s), 3.57 (3H, s), 6.88 (1H, s), 7.17 (1H, d, J = 7.7 Hz), 7.35 (2H, t, J = 8.9Hz), 7.45 (1H, t, J =7.9Hz), 7.63 (1H, t, J = 7.7Hz), 7.8-8.1 (6H, m), 8.21 (1H, s), 10.43 (1H, s)

ESI- Mass m/z : 386 (M^++1).

Preparation 16(1)

To a suspension of 2-bromo-5-methoxycarbonylthiophene (1.11 g), 4-fluorophenylboronic acid (0.91 g) and tetrakis(triphenylphosphine)palladium (289 mg) in 1,2-dimethoxyethane

(10 ml) was added aqueous solution of sodium carbonate (2M, 6.5 ml) followed by stirring at 80℃ for 6 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 30% dichloromethane in n-hexane to give 2-methoxycarbonyl-5-(4-fluorophenyl)thiophene (1.16 g, 98.3 %).
NMR ($CDCl_3$, δ): 3.86 (3H, s), 7.32 (2H, t, J = 8.8Hz), 7.59 (1H, d, J = 4.0Hz), 7.7-7.9 (3H, m)
APCI- Mass m/z : 237 (M^++1).

Preparation 16(2)

To a solution of 2-methoxycarbonyl-5-(4-fluorophenyl)thiophene (1.15 g) in methanol (10 ml) and tetrahydrofuran (10 ml) was added an aqueous solution of sodium hydroxide (1N, 7.3 ml) followed by stirring at 60℃ for 3 hours. To the mixture was added hydrochloric acid (1N, 8 ml). The resulting precipitate was collected by filtration and dried to give 5-(4-fluorophenyl)thiophene-2-carboxylic acid (1.06 g, 98.1 %).
NMR (DMSO-d_6, δ): 7.30 (2H, t, J =8.8Hz), 7.55 (1H, d, J = 4.4Hz), 7.7-7.9 (3H, m)
ESI- Mass m/z : 223 (M^++1).

Example 16

To a suspension of 5-(4-fluorophenyl)thiophene-2-carboxylic acid (156 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (131 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg) and 4-dimethylaminopyridine (43 mg). The mixture was stirred at ambient temperature for 72 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-5-(4-fluorophenyl)thiophene-2-carboxamide (240 mg, 88.9 %).

NMR (DMSO-d_6, δ): 2.36(3H, s), 3.56 (3H, s), 6.88 (1H, s), 7.17 (1H, d, J = 7.8 Hz), 7.31 (2H, t, J = 8.9Hz), 7.44 (1H, t, J =7.9Hz), 7.61 (1H, d, J = 4.0Hz), 7.72 (1H, d, J = 8.0Hz), 8.03 (1H, d, J =4.0Hz), 10.33 (1H, s)
APCI- Mass m/z : 392 (M^++1).

Example 17

To a suspension of 2,3-dimethylindole-7-carboxylic acid (95 mg) and 1-hydroxybenzotriazole (81 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg), and the mixture was stirred for 5 minutes. After adding 3-(pyrimidin-5-yl)aniline (94 mg) and 4-dimethylaminopyridine (92 mg), the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-(3-(pyrimidin-5-yl)-phenyl)-2,3-dimethyl-1H-indole-7-carboxamide (117 mg, 68.4 %).
NMR (DMSO-d_6, δ): 2.19 (3H, s), 2.37 (3H, s), 7.10 (1H, t, J = 7.6Hz), 7.5-7.7 (2H, m), 7.63 (1H, d, J =7.7Hz), 7.77 (1H, d, J =7.7Hz), 7.9-8.0 (1H, m), 8.30 (1H, s), 9.13 (2H, s), 9.23 (1H, s), 10.38 (1H, s), 10.81 (1H, s)
APCI- Mass m/z : 343 (M^++1).

Example 18

To a suspension of 9H-carbazole-1-carboxylic acid (112 mg) and 3-(1,3,4-triazol-1-yl)aniline (147 mg) in dichloromethane (3 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (188 mg) and 4-dimethylaminopyridine (43 mg). The mixture was stirred at ambient temperature for 24 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration and dried to give N-(3-([1,2,4]triazol-4-yl)phenyl)-

9H-carbazole-1-carboxamide (38 mg, 15.4 %).

NMR (DMSO-d_6, δ): 7.20 (1H, t, J =7.4Hz), 7.33 (1H, t, J =7.7 Hz), 7.3-7.5 (2H, m), 7.60 (1H, t, J =8.0Hz), 7.72 (1H, d, J = 8.0Hz), 7.89 (1H, d, J =8.4 Hz), 8.1-8.3 (3H, m), 8.40 (1H, d, J =7.5 Hz), 9.09 (2H, s), 10.65 (1H, s), 11.54 (1H, s)

APCI- Mass m/z : 354 (M^++1).

Example 19

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 4-methyl-3-(pyrimidin-5-yl)aniline (93 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 24 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-[4-methyl-3-(pyrimidin-5-yl)-phenyl]-3-methyl-2-trifluoromethyl-1H-indole-7-carboxamide (155 mg, 75.6 %).

NMR (DMSO-d_6, δ): 2.28 (3H, s), 2.44 (3H, d, J =2.0Hz), 7.29 (1H, t, J = 7.7Hz), 7.3-7.4 (1H, m), 7.8-8.0 (4H, m), 8.90 (2H, s), 9.24 (1H, s), 10.49 (1H, s), 11.44 (1H, s)

APCI- Mass m/z : 411 (M^++1).

Example 20

To a suspension of 2-trifluoromethyl-3-methylindole-7-carboxylic acid (122 mg) and 3-(1,2,4-triazol-1-yl)aniline (80 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (30 mg). The mixture was stirred at ambient temperature for 72 hours and diluted with dichloromethane. The solution was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration and

dried to give N-[3-(1,2,4-triazol-1-yl)-phenyl]-3-methyl-2-trifluoromethyl-1H-indole-7-carboxamide (97 mg, 50.3 %).
NMR (DMSO-d_6, δ): 2.45 (3H, d, J =2.0Hz), 7.31(1H, t, J = 7.7Hz), 7.5-7.7 (2H, m), 7.82 (2H, m), 8.27 (2H, s), 8.51 (1H, s), 9.29 (1H, s), 10.68 (1H, s), 11.53 (1H, s)
APCI- Mass m/z : 386 (M^++1).

Preparation 21(1)

A suspension of 5-bromopyrimidine(1.52 g),2-methylphenylboronic acid (1.43 g), sodium carbonate (3.04 g) and 10 % palladium on charcoal (50 % wet, 0.85 g) was refluxed for 24 hours. The mixture was filtered and the filtrate was concentrated under reduced pressure. To the residue ethyl acetate was added and the mixture was washed with water and brine. The separated organic layer was dried over magnesium sulfate and evaporated under pressure to give 5-(2-methylphenyl)pyrimidine (1.61 g, 98.7 %).
NMR (DMSO-d_6, δ): 2.27 (3H, s), 7.3-7.5 (4H, m), 8.87 (2H, s), 9.21 (1H, s)
APCI- Mass m/z : 171 (M^++1).

Preparation 21(2)

To a suspension of 5-(2-methylphenyl)pyrimidine (0.85 g) in concentrated sulfuric acid (10 ml) was portionwise added potassium nitrate (556 mg) at 5℃. The mixture was stirred at 5℃ for 30 minutes and poured into crushed ice. The pH of the mixture was adjusted to 8.0 with an aqueous sodium hydroxide solution (4N) and extracted with ethyl acetate. The organic layer was washed with water twice and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting precipitate was collected by filtration, washed with methanol and dried to give 5-(2-methyl-5-nitrophenyl)pyrimidine (662 mg,61.3 %).
NMR (DMSO-d_6, δ): 2.38 (3H, s), 7.68 (1H, d, J=8.2Hz), 8.2-8,4 (2H, m), 8.96 (2H, s), 9.28 (1H, s)
APCI- Mass m/z : 216 (M^++1).

Preparation 21(3)

A suspension of 5-(2-methyl-5-nitrophenyl)pyrimidine (0.431 g) in tetrahydrofuran (4 ml) and methanol (4 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 129 mg) under hydrogen atmosphere for 2 hours. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give 5-(5-amino-2-methylphenyl)pyrimidine (370 mg, 99.7 %).

NMR (DMSO-d_6, δ): 2.07 (3H, s), 5.05 (2H, s), 6.48 (1H, d, J =2.4Hz), 6.58 (1H, dd, J =8.0Hz, 2.4 Hz), 6.99 (1H, d, J =8.0Hz), 8.78 (2H, s), 9.16 (1H, s)

APCI- Mass m/z : 186 (M^++1).

Example 21

To a suspension of 4-methyl-3-(pyrimidin-5-yl)aniline (0.111 g) and pyridine (0.15 ml) in dichloromethane (2 ml) was dropwise added a solution of the fluorene-1-carbonyl chloride (0.137 g) in dichloromethane (2 ml) followed by stirring for 2 hours. The mixture was diluted with dichloromethane and washed with an aqueous solution of sodium hydrogen carbonate and brine. The separated organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was triturated with methanol. The resulting solid was collected by filtration to give N-(4-methyl-3-(pyrimidin-5-yl)-phenyl)-9H-fluorene-1-carboxamide (0.167 g, 73.9 %).

NMR (DMSO-d_6, δ): 2.25 (3H, s), 4.20 (2H, s), 7.3-7.5 (2H, m), 7.5-7.7 (2H, m), 7.7-7.9 (2H, m), 7.97 (1H, d, J= 6.5 Hz), 8.11 (1H, d, J =7.1Hz), 8.90 (2H, s), 9.24 (1H, s), 10.41 (1H, s)

APCI- Mass m/z : 378 (M^++1).

Example 22

To a suspension of 9H-carbazole-1-carboxylic acid (148 mg) and 1-hydroxybenzotriazole (130 mg) in dichloromethane (3 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (201 mg) and the mixture was stirred for 5 minutes. After adding 4-methyl-3-

(pyrimidin-5-yl)aniline (130 mg) and 4-dimethylaminopyridine (128 mg), the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 2% methanol in dichloromethane to give N-(4-methyl-3-(pyrimidin-5-yl)-phenyl)-9H-carbazole-1-carboxamide (140 mg, 52.8 %).

NMR (DMSO-d_6, δ): 2.28 (3H, s), 7.20 (1H, t, J =7.4 Hz), 7.31 (1H, t, J =7.8Hz), 7.3-7.5 (2H, m), 7.70 (1H, d, J = 8.0Hz), 7.86 (1H, d , J= 8.2Hz), 7.95 (1H, d, J = 2.0Hz), 8.15 (2H, t, J =7.4 Hz), 8.37 (1H, d, J =7.6Hz), 8.93 (2H, s), 9.25 (1H, s), 10.47 (1H, s), 11.52 (1H, s)

APCI- Mass m/z : 379 (M^++1).

Preparation 23

To a suspension of 2,2'-bithiophene (1.0 g) in tetrahydrofuran (10 ml) was added a solution of n-butyl lithium in n-hexane (1.54 M, 4.3 ml) at -25℃ under nitrogen atmosphere. The mixture was stirred at -60℃ for 30 minutes. To the solution dry-ice (1.0 g) was added and the mixture was stirred at ambient temperature for 30 minutes. To the resultant suspension hydrochloric acid (1N, 10 ml) and ethyl acetate were added. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with diisopropyl ether. The resulting precipitate was collected by filtration, washed with diisopropyl ether and dried to give [2,2']bithiophenyl-5-carboxylic acid (952 mg, 75.6 %).

NMR (DMSO-d_6, δ): 7.14 (1H, t, J = 4.3Hz), 7.35 (1H, d, J = 3.8Hz), 7.4-7.8 (3H, m), 12.5-13.5 (1H, broad s)

APCI- Mass m/z : 211 (M^++1).

Example 23

To a suspension of [2,2']bithiophenyl-5-carboxylic acid (105 mg) and 1-hydroxybenzotriazole (81 mg) in dichloromethane (2 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

(144 mg) and the mixture was stirred for 15 minutes. After adding 3-(1,2-dimethylimidazol-5-yl)aniline (94 mg) and 4-dimethylaminopyridine (92 mg), the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by a silica gel column chromatography eluting with 3% methanol in dichloromethane to give N-[3-(2,3-dimethyl-3H-imidazol-4-yl)-phenyl]-[2,2']bithiophenyl-5-carboxamide (117 mg, 61.6 %).

NMR (DMSO-d_6, δ): 2.36(3H, s), 3.54 (3H, s), 6.88 (1H, s), 7.1-7.2 (2H, m), 7.4-7.6 (3H, m), 7.62 (1H, dd, J = 5.1Hz, 1.1 Hz), 7.7-7.9 (2H, m), 7.99 (1H, d, J =4.0Hz), 10.33 (1H, s)

APCI- Mass m/z : 380 (M^++1).

Example 24

N-(3-(Imidazol-1-yl)phenyl)-1-phenylpyrrole-3-carboxamide was prepared in a manner similar to Example 12.

mp: 100-103℃ (diisopropyl ether/ethyl acetate)

IR (KBr, ν): 1645 cm^{-1}

NMR (DMSO-d_6, δ): 6.88 (1H, s), 7.13 (1H, s), 7.30-7.80 (10H, m), 8.04 (1H, s), 8.10-8.20 (2H, m), 9.89 (1H, s).

Mass m/z : 329 (M^++1).

Example 25

To 2-phenylthiazole-4-carboxylic acid (70 mg) in 5 mL benzene was added thionyl chloride(0.075 mL) at room temperature. The mixture was heated under reflux for an hour. The mixture was cooled and evaporated under reduced pressure. To the mixture added was dichloromethane (10ml) followed by 3-(imidazol-1-yl)aniline (54 mg) and triethylamine (0.1 ml). The mixture was stirred at room temperature for an hour. The mixture was washed with a saturated aqueous sodium bicarbonate solution, dried with sodium sulfate and evaporated. The residue was recrystallized from diisopropyl ether/ethyl acetate to give N-(3-(imidazol-1-yl)phenyl)-2-phenylthiazole-4-carboxamide.

mp: 131-134℃

IR (nujol, ν): 1665cm^{-1}

NMR (DMSO-d_6, δ): 7.14 (1H, s), 7.42 (1H, d, J=9 Hz), 7.45-7.60 (4H, m), 7.72 (1H, s), 7.94 (1H, d, J=8 Hz), 8.10-8.25 (4H, m), 8.54 (1H, s), 10.41 (1H, s)

Mass m/z : 347 (M^++1).

Preparation 26 (1)

To a suspension of m-nitroaniline (2.0 g), phosphoric acid (1.67 ml), butane-2,3-dione (1.27 ml) and an aqueous solution of formaldehyde (35 % w/w, 1.24 ml) in water (15 ml) was added an aqueous solution of ammonium chloride (5M, 6 ml) dropwise at 100℃. After stirring for 2 hours at 100℃, the mixture was poured into an aqueous saturated sodium hydrogen carbonate solution. The mixture was extracted with ethyl acetate. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified with a silica gel column chromatography eluting with 0-3 % methanol/dichloromethane to give 4,5-dimethyl-1-(3-nitrophenyl)imidazole (135 mg, 4.3 %).

APCI-mass m/z : 218 (M^+-1)

NMR (DMSO-d_6, δ); 2.12 (3H, s), 7.7-7.9 (3H, m), 8.23 (1H, t, J=2.1 Hz), 8.28 (1H, dd, J=1.5Hz, 8.0Hz).

Preparation 26 (2)

A suspension of 4,5-dimethyl-1-(3-nitrophenyl)imidazole (130 mg) in methanol (2 ml) and tetrahydrofuran (2 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 50 mg) under hydrogen atmosphere for 3 hours. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give 3-(4,5-dimethyl-imidazol-1-yl)aniline (110 mg, 98.2 %).

APCI-Mass 188 (M^++1)

NMR (DMSO-d_6, δ) ; 2.05 (3H, s), 2.08 (3H, s), 5.39 (2H, s), 6.43(1H, d, J=7.6 Hz), 6.48 (1H, s), 6.60 (1H, d, J=8.1 Hz), 7.12 (1H, t, J=8.0 Hz),

7.52 (1H, s).

Preparation 26 (3)

To a suspension of N-formyl-3-nitroaniline (831 mg) and potassium carbonate (830 mg) in N,N-dimethylformamide (5 ml) was added 2-bromo-3-butanone (906 mg), and the mixture was stirred for 72 hours. The mixture was diluted with ethyl acetate and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated to give N-(1-methyl-2-oxo-propyl)-N-(3-nitrophenyl)formamide (1.18 g, 100 %).

APCI-Mass m/z :237 (M^++1)

NMR (DMSO-d_6, δ) ; 1.35 (3H, d, J=7.1 Hz), 2.18 (3H, s), 4.79 (1H, q, J=7.1 Hz); 7.74 (1H, t, J=8.2 Hz), 7.83 (1H, d, J=8.2 Hz), 8.1-8.2 (2H, m), 8.48 (1H, s)

Preparation 26 (4)

A suspension of N-(1-methyl-2-oxo-propyl)-N-(3-nitrophenyl)formamide (1.17 g), ammonium acetate (3.82 g) and acetic acid (1 ml) in xylene (20 ml) was refluxed for 2 hours. After adding ethyl acetate and an aqueous solution of sodium hydroxide (1N, 100 ml), the mixture was stirred for 10 minutes. The separated aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified with a silica gel column chromatography eluting with 1-3 % methanol/dichloromethane to give 4,5-dimethyl-1-(3-nitrophenyl)imidazole (0.79 g, 73.1 %).

APCI-Mass m/z :218 (M^++1)

NMR (DMSO-d_6) δ ; 2.13 (6H, s), 7.7-8.0 (3H, m), 8.23 (1H, t, J=2.1 Hz), 8.28 (1H, dd, J=1.5 Hz, 8.0 Hz).

Example 26

To a suspension of 9H-carbazole-1-carboxylic acid (116 mg) and 3-(4,5-dimethylimidazol-1-yl)aniline (103 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

hydrochloride (158 mg) and 4-dimethylaminopyridine (101 mg), and the mixture was stirred for 20 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. After trituration with methanol, the residue was collected by filtration and dried to give N-[3-(4,5-dimethylimidazol-1-yl)-phenyl]-9H-carbazole-1-carboxamide (86 mg, 41.1 %).

APCI-mass m/z : 381 (M^++1)

NMR (DMSO-d_6) δ ; 2.14 (6H, s), 7.1-7.3 (2H, m), 7.32 (1H, t, J=7.6 Hz), 7.42 (1H, t, J=7.3 HZ), 7.55 (1H, t, J=8.0 Hz), 7.66 (1H, s), 7.70 (1H, d, J=8.0 Hz), 7.92 (1H, d, J=8.0 Hz), 8.00 (1H, s), 8.12 (1H, d, J=7.6 Hz), 8.18 (1H, d, J=7.6 Hz), 8.40 (1H, d, J=7.6 Hz), 10.60 (1H, s), 11.50 (1H, s).

Preparation 27 (1)

To a suspension of N-formyl-3-nitroaniline (1.0 g) in N,N-dimethylformamide (10 ml) was added sodium hydride (60 % dispersion in mineral oil, 264 mg), and the mixture was stirred for 20 minutes under nitrogen atmosphere. After a solution of 1-chloropropan-2-one (0.573 ml) in N,N-dimethylformamide (5 ml) was added dropwise to the mixture, the mixture was stirred for 2 hours and diluted with ethyl acetate and water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified with a silica gel column chromatography eluting with 2 % methanol in dichloromethane to give N-(3-nitrophenyl)-N-(2-oxo-propyl)-formamide (280 mg, 21.0 %).

APCI-Mass m/z : 223 (M^++1)

NMR (DMSO-d_6, δ) ; 2.19 (3H, s), 4.78 (2H, s), 7.6-7.8 (2H, m), 8.1-8.2 (2H, m), 8.73 (1H, s).

Preparation 27 (2)

A suspension of N-(3-nitrophenyl)-N-(2-oxo-propyl)-formamide (265 mg), ammonium acetate (919 mg) and acetic acid (0.3 ml) in xylene (5 ml) was refluxed for 2.5 hours and then evaporated under reduced

pressure. To the residue were added ethyl acetate and an aqueous solution of sodium hydroxide (1N, 25 ml), and the mixture was stirred for 10 minutes. The separated organic layer was washed with water and brine, dried over magnesium sulfate and evaporated to give 4-methyl-1-(3-nitrophenyl)imidazole (203 mg, 83.9 %).

APCI-Mass m/z :204 (M^++1)

NMR (DMSO-d_6, δ) ; 2.17 (3H, s), 7.65 (1H, s), 7.78 (1H, t, J=8.2 Hz), 8.1-8.2 (2H, m), 8.36 (1H, d, J=3.1 Hz), 8.44 (1H, t, J=2.2 Hz).

Preparation 27 (3)

A suspension of 4-methyl-1-(3-nitrophenyl)imidazole (198 mg) in methanol (2 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 100 mg) under hydrogen atmosphere for 2 hours. After the catalyst was filtered off, the filtrate was evaporated under reduced pressure to give 3-(4-methyl-imidazol-1-yl)aniline (162 mg, 95.9 %).

APCI-Mass m/z : 174 (M^++1)

NMR (DMSO-d_6, δ); 2.14 (3H, s), 5.35 (2H, s), 6.51 (1H, d, J=7.0 Hz), 6.6-6.8 (2H, m), 7.09 (1H, t, J=7.8 Hz), 7.23 (1H, s), 7.91 (1H, d, J=1.2 Hz).

Example 27

To a suspension of 9H-fluorene-1-carboxylic acid (79 mg) and 3-(4-methylimidazol-1-yl)aniline (65 mg) in dichloromethane (2 ml) was added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (101 mg) and 4-dimethylaminopyridine (23 mg), and the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane, washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol, and the insoluble material was collected by filtration and dried to give N-[3-(4-methylimidazol-1-yl)-phenyl]-9H-fluorene-1-carboxamide (40 mg, 29.2 %).

APCI-mass m/z : 366 (M^++1)

NMR (DMSO-d_6) δ ; 2.18 (3H, s), 4.21 (2H, s), 7.3-7.8 (9H, m), 7.98 (1H, d, J=6.5 Hz), 8.0-8.1 (2H, m), 8.13 (1H, d, J=7.3 Hz), 10.53 (1H, s).

Example 28

To a suspension of 9H-fluorene-1-carboxylic acid (106 mg) and 3-(4,5-dimethylimidazol-1-yl)aniline (94 mg) in dichloromethane (2 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (135 mg) and 4-dimethylaminopyridine (31 mg), and the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol, and the insoluble material was collected by filtration and dried to give N-[3-(4,5-dimethylimidazol-1-yl)-phenyl]-9H-fluorene-1-carboxamide (123 mg, 64.7 %).

APCI-mass m/z : 380 (M^++1)

NMR (DMSO-d_6, δ) ; 2.13 (6H, s), 4.20 (2H, s), 7.15 (1H, d, J=8.4 Hz), 7.3-7.5 (6H, m), 7.75 (1H, d, J=6.9 Hz), 7.8-7.9 (2H, m), 7.98 (1H, d, J=6.6 Hz), 8.13 (1H, d, J=6.9 Hz), 10.57 (1H, s).

Example 29

To a suspension of 3-(2-thienyl)benzoic acid (103 mg) and 3-(4,5-dimethylimidazol-1-yl)aniline (94 mg) in dichloromethane (2 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (135 mg) and 4-dimethylaminopyridine (31 mg), and the mixture was stirred for 24 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with methanol, and the insoluble material was collected by filtration and dried to give N-[3-(4,5-dimethylimidazol-1-yl)-phenyl]-3-(2-thienyl)benzamide (117 mg, 62.6 %).

APCI-mass m/z : 374 (M^++1)

NMR (DMSO-d_6, δ) ; 2.12 (6H, s), 7.1-7.3 (2H, m), 7.52 (1H, t, J=8.0 Hz), 7.6-7.8 (4H, m), 7.8-8.0 (4H, m), 8.18 (1H, s), 10.57 (1H, s).

Preparation 30 (1)

To a solution of N-(4-fluorophenyl)-2,2-dimethylpropionamide

(195 mg) in tetrahydrofuran (2 ml) was added a solution of n-butyl lithium in n-hexane (1.54M, 1.5 ml) dropwise at 0℃ under nitrogen atmosphere, and the mixture was stirred for 2 hours at 0℃. To the reaction mixture was added triisopropyl borate (0.692 ml) at - 40℃, and the mixture was stirred for 30 minutes at ambient temperature. To the mixture was added 1N-hydrochloric acid (3 ml), and the mixture was diluted with ethyl acetate and water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. To the residue were added methyl 3-bromo-2-fluorobenzoate (117 mg), tetrakis(triphenylphosphine)palladium (29 mg), an aqueous solution of sodium carbonate (2M, 2 ml) and 1,2-dimethoxyethane (5 ml). The resulting mixture was stirred under nitrogen atmosphere for 48 hours at 75℃, and diluted with ethyl acetate and water. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified with a silica gel column chromatography eluting with 20 % ethyl acetate/n-hexane to give 2'-(2,2-dimethylpropionamido)-2,5'-difluoro-biphenyl-3-carboxylic acid methyl ester (106 mg, 60.9 %).

APCI-mass m/z : 348 (M^++1)

NMR (DMSO-d_6, δ) ; 0.96 (9H, s), 3.85 (3H, s), 7.2-7.4 (4H, m), 7.52 (1H, dt, J=2.0 Hz, 7.1 Hz), 7.86 (1H, dt, J=1.9 Hz, 7.3 Hz), 8.92 (1H, s).

Preparation 30 (2)

A mixture of 2'-(2,2-dimethyl-propionamido)-2,5'-difluoro-biphenyl-3-carboxylic acid methyl ester (92 mg) and pyridinium chloride (3.0 g) was stirred for 3 hours at 200℃, and then poured into ice-water. The suspension was stirred for 10 minutes. The precipitate was collected by filtration, washed with water and dried to give 6-fluoro-9H-carbazole-1-carboxylic acid (46 mg, 76.7 %).

ESI-mass m/z : 228 (M^+-1)

NMR (DMSO-d_6, δ) ; 7.2-7.4 (2H, m), 7.73 (1H, dd, J=4.6 Hz, 8.9 Hz), 8.0-8.1 (2H, m), 8.42 (1H, d, J=7.3 Hz), 11.38 (1H, s), 13.19 (1H, broad s).

Preparation 30 (3)

A suspension of 3-bromonitrobenzene (20.2 g), 1,2-dimethyl-1H-imidazole (19.2 g), palladium acetate (1.12 g) and potassium carbonate (27.6 g) in N,N-dimethylformamide (500 ml) was stirred under nitrogen atmosphere for 24 hours at 140℃, and evaporated under reduced pressure. The residue was diluted with ethyl acetate and washed with water three times. The separated organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure to give 3-(1,2-dimethyl-imidazol-1-yl)nitrobenzene (19.2 g).

APCI-Mass m/z : 218 (M^++1)

NMR (DMSO-d_6, δ) ; 2.37(3H, s), 3.58 (3H, s), 7.09 (1H, s), 7.74 (1H, t, J=7.9 Hz), 7.91 (1H, d, J=7.7 Hz), 8.1-8.3 (2H, m).

Preparation 30 (4)

A suspension of 3-(1,2-dimethyl-1H-imidazol-5-yl)nitrobenzene (19.2 g) in methanol (200 ml) was hydrogenated over palladium on carbon (10 % w/w, 50 % wet, 5 g) under hydrogen atmosphere for 10 hours. After the catalyst was filtered off, the filtrate was evaporated under reduced pressure. The residue was triturated with ethyl acetate and diisopropyl ether to give 3-(1,2-dimethyl-imidazol-5-yl)aniline (14.65 g).

APCI-Mass m/z : 188 (M^++1)

NMR (DMSO-d_6, δ) ; 2.32 (3H, s), 3.49 (3H, s), 5.16 (2H, s), 6.5-6.7 (3H, m), 6.73 (1H, s), 7.07 (1H, t, J=7.7 Hz).

Example 30

To a suspension of 6-fluoro-9H-carbazole-1-carboxylic acid (37 mg) and 3-(1,2-dimethylimidazol-5-yl)aniline (43 mg) in dichloromethane (1 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (53 mg) and 4-dimethylaminopyridine (11 mg), and the mixture was stirred for 40 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate

and evaporated under reduced pressure. The residue was purified with a silica gel column chromatography eluting with 2-3 % methanol/dichloromethane to give N-[3-(1,2-dimethylimidazol-5-yl)-phenyl]-6-fluoro-9H-carbazole-1-carboxamide (38 mg, 51.4 %).

APCI-mass m/z : 399 (M^++1)

NMR (DMSO-d_6, δ) ; 2.37(3H, s), 3.59 (3H, s), 6.90 (1H, s), 7.2-7.4 (3H, m), 7.47 (1H, t, J=7.9 Hz), 7.70 (1H, dd, J=4.6 Hz, 8.9 Hz), 7.88 (1H, d, J=8.1 Hz), 7.95 (1H, s), 8.03 (1H, d, J=2.5 Hz, 9.4 Hz), 8.14 (1H, d, J=7.2 Hz), 8.40 (1H, d, J=7.6 Hz), 10.48 (1H, s), 11.55 (1H, s).

Preparation 31 (1)

To a suspension of 2-hydrazinobenzoic acid hydrochloride (2.0 g) in acetic acid (8 ml) was added dropwise a solution of 2-butanone (0.9 ml) in acetic acid (2 ml), and the resultant mixture was heated at 80 ℃ for one hour. After 6N-hydrochloric acid (8 ml) was added to the reaction mixture, the mixture was heated at 100 ℃ for 5 hours. The mixture was diluted with water (18 ml), and allowed to cool to 40 ℃. The resultant precipitate was collected by filtration, washed with a small amount of diisopropyl ether and dried *in vacuo* to give 2,3-dimethyl-1H-indole-7-carboxylic acid (0.78 g).

APCI-mass m/z : 190 (M^++1)

NMR (DMSO-d_6, δ); 2.17(3H, s), 2.36 (3H, s), 7.02 (1H, t, d=7.6 Hz), 7.63 (2H, d, d=7.6 Hz), 10.55 (1H, brs), 12.82 (1H, brs).

Example 31

To a suspension of 2,3-dimethyl-1H-indole-7-carboxylic acid (95 mg) and 3-(4,5-dimethylimidazol-1-yl)aniline (94 mg) in dichloromethane (2 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (135 mg) and 4-dimethylaminopyridine (31 mg), and the mixture was stirred for 12 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was triturated with dichloromethane, and the insoluble material was collected by

filtration and dried to give N-[3-(4,5-dimethyl-imidazol-1-yl)-phenyl]-2,3-dimethyl-1H-indole-7-carboxamide (77 mg, 43.0 %).
APCI-mass m/z : 359 (M^++1)
NMR (DMSO-d_6, δ) ; 2.12 (6H, s), 2.19 (3H, s), 2.36 (3H, s), 7.07 (1H, d, J=7.6 Hz), 7.1-7.2 (1H, m), 7.51 (1H, t, J=8.0 Hz), 7.62 (1H, d, J=7.6 Hz), 7.64 (1H, s), 7.72 (1H, d, J=7.4 Hz), 7.88 (1H, d, J=8.0 Hz), 7.96 (1H, t, J=2.0 Hz), 10.42 (1H, s), 10.77 (1H, s).

Example 32

To a suspension of 6-fluoro-9H-carbazole-1-carboxylic acid (70 mg) and 3-(4,5-dimethylimidazol-1-yl)aniline (60 mg) in dichloromethane (2 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (88 mg) and 4-dimethylaminopyridine (19 mg), and the mixture was stirred for 40 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified with a silica gel column chromatography eluting with 2-3 % methanol/dichloromethane to give N-[3-(4,5-dimethylimidazol-1-yl)-phenyl]-6-fluoro-9H-carbazole-1-carboxamide (65 mg, 53.7 %).
APCI-mass m/z : 399 (M^++1)
NMR (DMSO-d_6, δ) ; 2.14 (6H, s), 7.17 (1H, d, J=7.9 Hz), 7.3-7.5 (2H, m), 7.55 (1H, t, J=8.0 Hz), 7.6-7.8 (2H, m), 7.92 (1H, d, J=8.3 Hz), 8.0-8.1 (2H, m), 8.14 (1H, d, J=7.1 Hz), 8.41 (1H, d, J=7.5 Hz), 10.60 (1H, s), 11.56 (1H, s).

Example 33

To a suspension of 9H-carbazole-1-carboxylic acid (106 mg) and 3-(4-methylimidazol-1-yl)aniline (87 mg) in dichloromethane (5 ml) were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (144 mg) and 4-dimethylaminopyridine (31 mg), and the mixture was stirred for 40 hours. The mixture was diluted with dichloromethane and washed with water and brine. The mixture was dried over magnesium sulfate and evaporated under reduced pressure. The

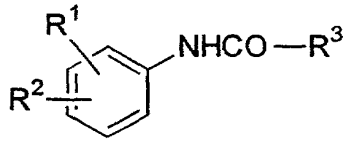
residue was triturated with methanol, and the insoluble material was collected by filtration and dried to give N-[3-(4-methylimidazol-1-yl)-phenyl]-9H-carbazole-1-carboxamide (68 mg, 37.0 %).

APCI-mass m/z : 367(M^{+}+1)

NMR (DMSO-d_6, δ) ; 2.19 (3H, s), 7.20 (1H, t, J=7.5 Hz), 7.3-7.5 (4H, m), 7.52 (1H, t, J=8.0 Hz), 7.72 (1H, d, J=8.0 Hz), 7.80 (1H, d, J=8.4 Hz), 8.09 (1H, d, J=9.2 Hz), 8.2-8.3 (3H, m), 8.40 (1H, d, J=7.6 Hz), 10.56 (1H, s), 11.53 (1H, s).

CLAIMS

1. An amide compound of the formula (I):



(I)

wherein

R^1 is an N-containing heterocyclic group selected from an imidazolyl, a triazolyl, a pyridyl, a pyridazinyl, a pyrimidinyl and a pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R^2 is a hydrogen atom or a lower alkyl group, and

R^3 is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group,

provided that

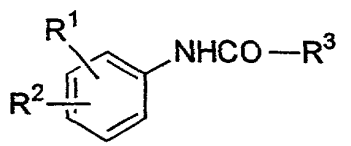
(1) the imidazolyl group for R^1 is substituted with one or more alkyl groups, when R^3 is a phenyl group substituted thienyl; an indolyl group substituted with lower alkyl; or carbazolyl group,

(2) the imidazolyl group for R^1 is substituted with two lower alkyl groups, when R^3 is a phenyl group substituted with halophenyl, or

(3) R^1 is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, a 4-(lower alkyl)-imidazol-1-yl or a 4,5-di(lower alkyl)-imidazol-1-yl group, when R^3 is fluorenyl group

and its salt.

2. A pharmaceutical composition comprising an amide compound of the formula (I):



(I)

wherein

R^1 is an N-containing heterocyclic group selected from an imidazolyl, a triazolyl, a pyridyl, a pyridazinyl, a pyrimidinyl and a pyrazinyl group, each of which may be substituted with one or more lower alkyl groups,

R^2 is a hydrogen atom or a lower alkyl group, and

R^3 is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group,

provided that

(1) the imidazolyl group for R^1 is substituted with one or more alkyl groups, when R^3 is a phenyl group substituted thienyl; an indolyl group substituted with lower alkyl; or carbazolyl group,

(2) the imidazolyl group for R^1 is substituted with two lower alkyl groups, when R^3 is a phenyl group substituted with halophenyl, or

(3) R^1 is pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, a 4-(lower alkyl)-imidazol-1-yl or a 4,5-di(lower alkyl)-imidazol-1-yl group, when R^3 is fluorenyl group

or its non-toxic pharmaceutically acceptable salt.

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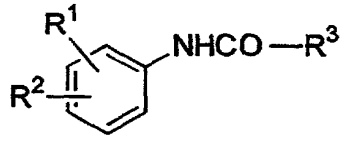
(54) Title: AMIDE COMPOUNDS



(I)

(57) Abstract: Amide compounds of formula (I) wherein R^1 is an N-containing heterocyclic group selected from imidazolyl, triazolyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl, each of which may be substituted with one or more lower alkyl groups, R^2 is a hydrogen atom or a lower alkyl group, and R^3 is a phenyl group substituted with thienyl or halophenyl; a thienyl group substituted with thienyl, phenyl or halophenyl; a pyrrolyl group substituted with phenyl; a thiazolyl group substituted with phenyl; an indolyl group substituted with lower alkyl and/or halo(lower)alkyl; a fluorenyl group; or a carbazolyl group, and salts thereof which have 5-HT antagonism activity.

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

AMIDE COMPOUNDS

the specification of which

- ☐ is attached hereto.
- ☐ was filed on _____ as
  Application Serial No. _____
  and amended on _____.
- ☒ was filed as PCT international application
  Number PCT/JP00/06623
  on September 26, 2000,
  and was amended under PCT Article 19
  on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
PQ3198	Australia	01/10/1999	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number) (Filing Date)

(Application Number) (Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or under § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)

And we (I) hereby appoint the following registered practitioner(s):

022850

as our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to

022850

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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